Tissue Hypoxia: Implications for the Respiratory Clinician

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Summary

Oxygen is essential for normal aerobic metabolism in mammals. Hypoxia is the presence of lower than normal oxygen content and pressure in the cell. Causes of hypoxia include hypoxemia (low blood oxygen content and pressure), impaired oxygen delivery, and impaired cellular oxygen uptake/utilization. Many compensatory mechanisms exist at the global, regional, and cellular levels to allow cells to function in a hypoxic environment. Clinical management of tissue hypoxia usually focuses on global hypoxemia and oxygen delivery. As we move into the future, the clinical focus needs to change to assessing and managing mission-critical regional hypoxia to avoid unnecessary and potential toxic global strategies. We also need to focus on understanding and better harnessing the body's own adaptive mechanisms to hypoxia. *Key words: hypoxia; hypoxemia; alveolar ventilation; ventilation/perfusion matching; diffusion; hemoglobin binding; hemoglobin-oxygen binding; regional oxygenation; oxygen extraction; oxygen utilization; hypoxia-inducible factors.* [Respir Care 2014;59(10):1590–1596. © 2014 Daedalus Enterprises]

Introduction

Oxygen is essential for normal aerobic metabolism in mammals.[1-3] The key reaction occurs in the mitochondria of cells and involves combining a fuel (eg, sugars, fats) with oxygen to produce energy (converting adenosine 5′-diphosphate to adenosine 5′-triphosphate) along with CO_2 and H_2O. Hypoxia is a state of low oxygen content and partial pressure in the cell. Depending upon the cell type, its metabolic demands, and its ability to adapt to hypoxia, the response to various levels of hypoxia can range from substantial adaptation to cell death.[4,5] The discussion below will focus on 3 areas: (1) causes of hypoxia, (2) physiologic responses/adaptations to hypoxia (global, regional, and cellular), and (3) current and future clinical implications.

Causes of Hypoxia

Tissue hypoxia can be caused by one of 3 general abnormalities: hypoxemia, impaired oxygen delivery to tissues, and impaired tissue oxygen extraction/utilization. Each will be addressed separately.

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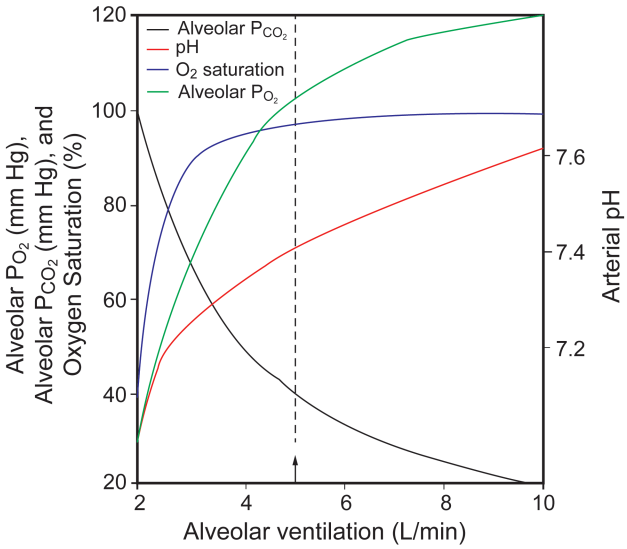

Fig. 1. Plots of alveolar P_{O_2}, hemoglobin saturation, and alveolar P_{CO_2} as a function of alveolar ventilation in a normal subject at sea level (inspired oxygen pressure of 150 mm Hg). The dashed line indicates normal values. Adapted from Reference 2.

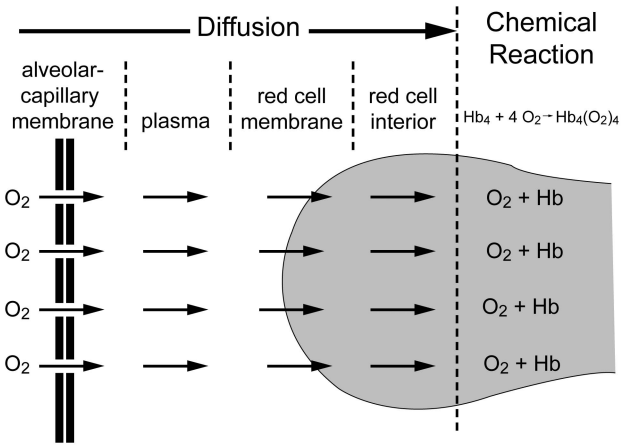

Fig. 2. Depiction of the various barriers oxygen must traverse as it moves from the alveolar space to ultimately combine with hemoglobin (Hb) in the red blood cell. Adapted from Reference 6.

Hypoxemia

Hypoxemia refers to low oxygen content in arterial blood, and there are several factors that impact this state.[1-3] The first is the oxygen content of inspired gas. At sea level, the inspired P_{O_2} is ~150 mm Hg. Inspired P_{O_2} falls progressively with altitude and nadirs at 43 mm Hg at the summit of Mt Everest (29,028 feet).

Alveolar ventilation is the next step in oxygenating blood. As alveolar ventilation increases, alveolar P_{O_2} (P_{AO_2}) rises logarithmically and assymptotes on the inspired P_{O_2} (Fig. 1).[2] From Figure 1, it can be seen that in a normal human at rest with an inspired P_{O_2} of 150 mm Hg, an alveolar ventilation near normal (eg, 5 L/min) provides a P_{AO_2} of 100 mm Hg, a pressure adequate to fully saturate hemoglobin (Hb). Importantly, because oxygen is poorly soluble in plasma, once Hb is fully saturated, increasing alveolar ventilation further adds little to blood oxygen content (Fig. 1). This is in contrast to P_{CO_2}, which continues to decrease in both blood and alveolar gas as alveolar ventilation is progressively increased (Fig. 1).

Once oxygen is in the alveolar spaces, the matching of blood and alveolar gas is the next step in determining arterial oxygen content.[1-3] In normal humans at both rest and exercise, smooth muscles in both the airways and blood vessels ensure that ventilation/perfusion ($\dot{V}/\dot{Q}$) is matched nearly 1:1 in all alveolar-capillary units. In disease states, $\dot{V}/\dot{Q}$ relationships become deranged, and oxygen transport into blood is impaired. Similar to the phenomenon described in Figure 1, because of poor O_2 solubility in plasma, relative hyperventilation and 100% Hb saturation in high $\dot{V}/\dot{Q}$ units cannot make up for the unsaturated Hb coming from underventilated low $\dot{V}/\dot{Q}$ units. This is not the case for CO_2, where high $\dot{V}/\dot{Q}$ units can compensate for low $\dot{V}/\dot{Q}$ units. $\dot{V}/\dot{Q}$ inhomogeneities thus have less effect on P_{CO_2}.

Regardless of $\dot{V}/\dot{Q}$ matching, the next step in blood oxygenation is the diffusion of oxygen through the alveolar-capillary interface and plasma and then into the red blood cell cytoplasm, where it can bind with the Hb molecule (Fig. 2).[6] This can be expressed by the determinants for lung diffusing capacity (D_L): $1/D_L = 1/(D_M) + (1/V_c \times \theta)$, where DM is the membrane diffusing capacity reflecting the properties and surface areas of the alveolar-capillary interface, V_c is the capillary Hb volume, and θ is the binding rate of Hb to oxygen.[1-3,6]

In normal humans, the diffusion and Hb-binding process is time-dependent, and equilibration generally occurs over ~250 ms.[1-3,6] This is important because the normal transit time at rest for a red blood cell in the alveolar capillary is 500–750 ms, a time adequate for complete O_2 transfer. However, with extreme exercise and high pulmonary capillary blood flow, transit times may be shorter than 250 ms and produce hypoxemia. In disease states with abnormal alveolar-capillary structures and reduced P_{AO_2}, reduced membrane diffusing capacity and shorter transit times may both contribute to hypoxemia.

The final determinant of blood oxygen content is the amount of Hb in blood and its binding properties.[7] In normal humans, Hb approaches full saturation at a P_{O_2} of > 60–70 mm Hg. Tighter Hb binding to oxygen (a shift to the left in the oxyhemoglobin dissociation curve) means that lower levels of P_{O_2} are associated with near-complete saturation of Hb, and thus, tissue unloading is more difficult. Severe left shifting and functional loss of Hb can occur when oxygen-binding sites are impaired or blocked

Table 1. Differences in Blood Flow, O_2 Used, and Venous P_{O_2} of Selected Organs and Tissues

Tissue/Organ	Blood Flow		O_2 Used		Arteriovenous Oxygen Difference (mL of O_2/100 of mL Blood)	Venous Blood P_{O_2} (mm Hg)
	mL/min	% of $\dot{Q}_T$	mL/min	% of Total		
Heart	250	4	26.4	11	11.4	23
Skeletal muscle	1,200	21	72.0	30	8.4	34
Brain	750	13	48.0	20	6.3	33
Splanchnic (liver)	1,400	24	60.0	25	4.1	43
Kidneys	1,100	19	16.8	7	1.3	56
Skin	500	9	4.8	2	1.0	60
Other	600	10	12.0	5		
Total	5,800	100	240.0	100	4.1 (average)	46 (average)

Modified from Reference 3.
$\dot{Q}_T$ = cardiac output

(eg, methemoglobin, sulfhemoglobin, carboxyhemoglobin). On the other hand, a shift to the right of the curve means that at a given P_{O_2} less oxygen is bound to Hb, and this facilitates delivery of oxygen into the tissues. Normal values for oxygen content in blood with 150 g/L Hb are ~200 mL/L of blood.

Hypoxemia can be expressed in several ways. Typically, a P_{aO_2} of 60–80 mm Hg is considered mildly hypoxemic, whereas a P_{aO_2} of < 60 mm Hg is considered hypoxemia generally sufficient to warrant an intervention. These values can be referenced to the estimated P_{AO_2} (inspired oxygen pressure − P_{aCO_2}/respiratory quotient) and expressed as an alveolar-arterial oxygen difference ($P_{(A\text{-}a)O_2}$). This separates the effects of inspired oxygen pressure and alveolar ventilation (P_{AO_2}) from the effects of alveolar-capillary gas transport ($P_{(A\text{-}a)O_2}$) on hypoxemia. A normal $P_{(A\text{-}a)O_2}$ is a value less than one half your age, with a maximum of 25 mm Hg. Hypoxemia can also be expressed using arterial oxygen content, which incorporates both P_{aO_2} and Hb properties.

Oxygen Delivery

Oxygen delivery is the process of taking oxygenated blood from the alveolar capillaries to the tissues. Oxygen delivery depends on 2 factors: O_2 content and cardiac output. Mathematically, this is expressed as: $D_{O_2} = C_{aO_2} \times \dot{Q}_T$, where D_{O_2} is oxygen delivery, C_{aO_2} is blood O_2 content, and $\dot{Q}_T$ is cardiac output.

With a normal cardiac output of ~5 L/min and 200 mL of O_2/L of blood, this translates into a normal tissue oxygen delivery of ~1000 mL/min. Importantly, cardiac output can increase severalfold both under exercise conditions and in disease states (eg, sepsis, thyroid storm), resulting in the ability to deliver O_2 at 5,000–7,000 mL/min to tissues. In other disease states, O_2 delivery can be impaired by hypoxemia (low P_{aO_2} and/or low Hb) as well as low cardiac output.

Importantly, oxygen delivery is regulated by region. This facilitates oxygen delivery to regions that need it most.[1-3,6,7] Table 1 gives regional distributions of blood flow (and thus O_2 delivery) at rest. Under exercise conditions, blood flow to skeletal muscle can increase significantly, whereas blood flow to skin and intestines may decrease. Governing this distribution of oxygen delivery are both global factors (eg, adrenergic tone, systemic inflammatory mediators) and local factors, including local hypoxia, local cytokine production, local nitric oxide, vascular factors, and Hb properties.[8-11]

Oxygen Extraction/Utilization

Oxygen extraction/utilization is the process of moving oxygen from the Hb molecule into the cytoplasm of cells and ultimately into the mitochondria, where it is used for oxidative metabolism. This initially involves dissociation of O_2 from Hb and is affected by Hb-O_2 affinity (left shift and right shift of the Hb-O_2 dissociation curve as described above). Thereafter, it is largely a diffusive process, with a substantial gradient in P_{O_2} between capillary blood and mitochondria. This results in mitochondrial P_{O_2} of usually < 10 mm Hg.[3-5]

At rest, in the average tissue capillary bed, only 25% of the delivered oxygen content actually leaves the blood and enters the tissues (extraction ratio).[1-3,6,7] This means that for every 1,000 mL of oxygen delivered per min, 250 mL is extracted by the cells, and 750 mL remains in the blood. Thus, normal oxygen consumption is ~250 mL/min at rest, and mixed venous oxygen saturation is ~75%, which correlates with a mixed venous P_{O_2} of 40 mm Hg. Under exercise conditions, extraction can increase to 50% or even close to 60 or 75% in elite athletes, resulting in very low mixed venous oxygen contents. As with blood flow and oxygen delivery, oxygen extraction differs by tissue (see Table 1).

In the mitochondria, the final step of oxygen transport occurs when oxygen is combined with a fuel to produce energy in the cytochrome electron transport system.[1-3,12,13] A number of inflammatory disease states (eg, sepsis) are associated with disruptions in tissue extraction and mitochondrial utilization of oxygen.[8,9] Poisons such as cyanide can also directly block oxygen utilization in the mitochondria.[14] Under these conditions, mixed venous oxygen concentrations are often high.

Compensatory Mechanisms for Hypoxia

If tissue hypoxia occurs, global compensatory respiratory and cardiac mechanisms similar to those seen with exercise occur to improve oxygen delivery. Acutely, these include regional pulmonary vasoconstriction to improve $\dot{V}/\dot{Q}$ matching, hyperventilation to improve P_{AO_2}, acidosis-related right shifting of the oxyhemoglobin dissociation curve to facilitate O_2 unloading, and increases in cardiac output.[3-5] Over time, there is also an increase in red blood cell production, and this results in polycythemia in both subjects at altitude and in patients with chronic hypoxemia. Importantly, polycythemia can also increase blood viscosity and thus potentially impair blood flow and tissue oxygen delivery through capillaries. Indeed, subjects who adapt best to altitude dwelling have only a modest polycythemic response to hypoxemia.

Hypoxemia is also associated with an increase in red blood cell 2,3-diphosphoglycerate to facilitate O_2 unloading in the tissues.[5] If regional hypoxia is present (eg, regional ischemia, exercise, or inflammation), regional blood flow distributional changes also occur to direct blood flow to where oxygen delivery is needed most and away from regions that are less mission-critical.[5]

Regardless of the cause of hypoxia, at the cellular level, important adaptive mechanisms also exist. Central to all of these are hypoxia-inducible factors (HIFs), a group of heterodimeric proteins that interact with hundreds of genes in response to hypoxia.[15-20] HIF activation results in upregulation of erythropoietin, angiogenic factors, and vasoactive mediators; activation of glycolytic enzymes to produce anaerobic metabolism (with resulting lactate production); and even a mitochondrial hibernation-like phenomenon resulting in decreased oxygen demands.[15-24] HIFs can also down-regulate other processes in response to hypoxia.[15] All of these actions are designed to enhance cellular tolerance to hypoxia.

Experimentally, HIFs have been implicated as protective in a number of ischemic models. Examples include the phenomenon of cardiac ischemia preconditioning (which reduces experimental myocardial infarct size),[25,26] protection from the systemic effects of ischemic colitis,[27,28] and protection from limb ischemia.[29,30] HIFs have also been demonstrated to be increased in high altitude dwelling Tibetans[31] and to be crucial in fetal development.[32] Ironically, the angiogenesis properties of HIFs have also been related to accelerated tumor growth.[33] Recent work has implicated other cellular factors, including endogenous carbon monoxide and hydrogen sulfide, as mediators of intracellular hypoxic protection.[5]

In healthy individuals in hypoxemic environments, these compensatory mechanisms can be quite effective. Classic examples include the ability of humans to live at very high altitudes with a P_{aO_2} of ≤ 50 mm Hg[5,34,35] and stories of stowaways surviving in airplane landing gear assemblies for many hours at an altitude of 35,000 feet (CNN website, April 21, 2014). Similarly, the near-term fetus has a P_{aO_2} of < 30 mm Hg.[5,36] It is clear that, with proper compensatory mechanisms, mammalian cells can thrive with a P_{aO_2} lower than the traditional clinical thresholds of 55–60 mm Hg.

In diseased individuals, many of these compensatory mechanisms may be blunted. Systemic inflammation and organ dysfunction may impair ventilation, create poor $\dot{V}/\dot{Q}$ mismatching, limit cardiac function, disrupt proper control of systemic perfusion distribution, impair tissue oxygen extraction, and limit the Hb response.[8,9] Tolerance to low levels of O_2 and P_{aO_2} in disease states is thus likely to be reduced compared with healthy individuals. For example, an otherwise healthy individual in the ICU with low oxygen demands (eg, a hypothermic drowning victim) might be expected to tolerate much lower oxygenation levels than an elderly septic patient with high oxygen demands.

Current and Future Clinical Implications

Managing hypoxia traditionally involves efforts to improve oxygen delivery and focuses on blood oxygenation (P_{O_2} and Hb) and cardiac output. The relative value of manipulating each of these parameters is given in Table 2.[37] Importantly, each of these interventions has consequences.[38] Improving P_{O_2} usually involves supplemental oxygen and positive-pressure ventilation, which expose patients to risks of oxygen toxicity and ventilator-induced lung injury. Transfusions expose patients to fluid overload, immunologic risks, and possible transfusion-related lung injuries. Increasing cardiac output exposes patients to risks of fluid overload and excessive adrenergic stimulation. Thus, like so many interventions employed in critical care, improving the physiology of oxygen delivery may not translate into improved outcomes and must always be implemented cautiously.

An alternative way to manipulate tissue oxygenation is to manipulate oxygen consumption. On a global level, this can be done through pain management, fever control, agitation control, neuromuscular blockade, or cooling (eg, therapeutic hypothermia after cardiac arrest).[39,40] Indeed,

Table 2. Relative Effects of Changes in P_{aO_2}, Hb, and $\dot{Q}_T$ on D_{O_2}

	F_{IO_2}	P_{aO_2} (mm Hg)	S_{aO_2} (%)	Hb (g/L)	Dissolved O_2 (mL/L)	C_{aO_2} (mL/L)	$\dot{Q}_T$ (L/min)	D_{O_2} (mL/min)	D_{O_2} (% change)*
Normal†	0.21	97.5	96	130	3.0	170	5.3	900	0
Patient‡	0.21	45.0	75	70	1.4	72	4.0	288	− 68
↑ F_{IO_2}	0.35	67.5	92	70	2.1	88	4.0	352	+ 22
↑ ↑ F_{IO_2}	0.60	123.8	98	70	3.8	96	4.0	384	+ 9
↑ Hb	0.60	123.8	98	105	3.8	142	4.0	568	+ 48
↑ $\dot{Q}_T$	0.60	123.8	98	105	3.8	142	6.0	852	+ 50

$D_{O_2} = C_{aO_2} \times \dot{Q}_T$ mL/min, where D_{O_2} is oxygen delivery, C_{aO_2} is arterial oxygen content, and $\dot{Q}_T$ is cardiac output. $C_{aO_2} = (Hb \times S_{aO_2} \times 1.34) + (P_{aO_2} \times 0.23)$ mL/L, where Hb is hemoglobin, S_{aO_2} is arterial oxygen saturation, 1.34 mL is the volume of oxygen carried by 1 g of 100% saturated Hb, and $P_{aO_2} \times 0.23$ is the amount of oxygen in physical solution in 1 L of blood (which is < 3% of the total C_{aO_2} for normal P_{aO_2}, ie, < 105 mm Hg).

* Change in D_{O_2} expressed as a percentage of the preceding value

† Normal: subject (75 kg) at rest

‡ Patient: hypoxemia, anemia, reduced $\dot{Q}_T$, and evidence of global tissue hypoxia

the ability to survive at 35,000 feet in the wheel wells of a commercial aircraft as noted above was likely associated with hypothermia-induced hibernation of tissues. Each of these, to varying degrees, can lower O_2 demands in specific tissue beds to improve regional tissue oxygenation. However, these manipulations can have their own toxicities. For example, narcotics and anxiolytics can prolong the need for mechanical ventilation,[41] and neuromuscular blockade can lead to respiratory muscle disuse atrophy.[42] Whether hypothermia produces long-term injury is unknown.

As we move into the future, focus is needed in 2 areas. First, more direct assessments of regional hypoxia and an understanding of threshold levels for hypoxic injury in different regions are required.[43] This will allow us to better balance tradeoffs associated with conventional therapies. Second, future therapies need to address both regional manipulations of oxygen delivery and the development of strategies building upon the powerful compensatory mechanisms already present in cells.

Regarding assessments, the traditional way to quantify tissue hypoxia is to simplify and measure only global hypoxemia, oxygen delivery, and oxygen extraction. Commonly recommended therapeutic targets are a P_{aO_2} of > 55 mm Hg, Hb levels of at least 70 g/L (but perhaps as high as 90–100 g/L in high O_2 demand states), and cardiac indices (cardiac output referenced to body surface area) of > 2 L/min/m^2.[38]

However, oxygen utilization monitoring might offer more in-depth assessments of overall body oxygenation status than simple oxygen delivery. Using this approach, oxygen delivery could be deemed adequate if total body oxygen consumption was adequate (250 mL/min in a normal metabolic state: perhaps higher in sepsis, perhaps lower in the presence of paralytics). Indeed, a number of clinical studies in the last 2 decades argued that oxygen delivery should be increased until oxygen consumption is no longer increased.[44] However, because assessments of oxygen delivery and oxygen consumption utilize common variables (cardiac output and P_{aO_2} content), the use of simply the mixed venous P_{O_2} or mixed venous oxyhemoglobin saturation has been proposed as a more focused assessment of tissue oxygenation.[45,46] With this approach, a mixed venous P_{O_2} of > 40 mm Hg or mixed venous oxyhemoglobin saturation of > 70% (so-called goal-directed therapy)[47] might suggest the presence of adequate oxygen delivery. Importantly, these approaches assume that oxygen extraction capabilities are near normal, something that might not be present in a severe systemic inflammatory response state. Serum lactate has also been suggested as a monitor for global adequacy of oxygen delivery.[48]

It is clear from the discussion above that these global parameters are insensitive and nonspecific indicators of safe oxygenation at the regional tissue level. Thus, efforts to normalize these global values may force excessive use of potentially harmful support strategies.[38] However, current attempts to assess regional hypoxia are largely indirect through monitoring of specific organ functions. Examples include monitoring heart function (contractility, dysrhythmias), renal function (creatinine), liver function (liver metabolic properties and enzymes), and central nervous system function (mental status or seizures). If we are ever going to be comfortable with global permissive hypoxemia (ie, allowing a P_{aO_2} of < 55 mm Hg), regional assessments are going to be critical to guide therapy.[49-53]

Two organs for which direct venous or tissue P_{O_2} values are available are the brain and the intestine. The brain is a logical monitoring site, as it is the organ that is most sensitive to hypoxia.[5] Both animal and human studies suggest that an intracellular P_{O_2} in brain tissue of < 10–15 mm Hg is injurious.[54] Brain injury is also associated with oxyhemoglobin saturation of < 50–54% in blood sampled in the jugular venous system.[55] External probes placed on the forehead to measure oxidative state using

near-infrared technology are theoretically attractive but subject to artifacts from muscle metabolism on the scalp.[56]

The intestine is also an attractive site to monitor, as regional hypoxia there results in translocation of intestinal bacteria into blood. This conceptually feeds systemic inflammation and multiple organ failure.[57] Moreover, if intestinal oxygenation is thought to be adequate, other organs such as the brain are also likely to be adequate. Currently available monitors utilize intestinal luminal pH (P_{CO_2}) sensors to determine oxygenation adequacy.[57]

In future therapies, we will need a better understanding of how regional blood flow is modulated and how oxygen is extracted and utilized both under normal conditions and in disease states. We also need a better understanding of the remarkable compensatory mechanisms for hypoxia that exist and develop ways to harness them. Examples of future therapies might include Hb manipulations for more targeted blood flow and exploitation of HIF properties to better protect the hypoxic cell. The next decade should provide exciting new ways to support hypoxic patients.

Summary

Hypoxia is the presence of lower than normal oxygen content and pressure in the cell. Causes of hypoxia include hypoxemia (low blood oxygen content and pressure), impaired oxygen delivery, and impaired cellular oxygen uptake/utilization. Many compensatory mechanisms exist at the global, regional, and cellular levels to allow cells to function in a hypoxic environment. Clinical management of tissue hypoxia usually focuses on global hypoxemia and oxygen delivery. In the future, the clinical focus needs to change to assessing and managing regional hypoxia in critical organs to avoid unnecessary and potential toxic global strategies. We also need to focus on understanding and better harnessing the body's own adaptive mechanisms to hypoxia.

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